II. Remarks

Reconsideration of this application in view of the following remarks is respectfully requested. Claims 1, 3, 8-10, 12-27, 29-32, and 35-45 are currently pending. Claims 1 and 41 have been amended herein without prejudice. Support for the amendment can be found in the specification as originally filed, specifically at page 15, lines 14-24. It is respectfully submitted that no new matter has been added by virtue of this amendment.

A. Claim Rejections Under 35 U.S.C. § 112

In the Office Action, claims 1, 3, 8-10, 12-27, 29-32 and 35-45 were rejected under 35 U.S.C. §112, first paragraph for allegedly failing to comply with the written description requirement. Specifically, the Examiner stated that the phrases "opioid agonist" and "opioid antagonist" are not supported, as "there is no evidence that there is any per se structure/function relationship between disclosed opioid agonists, opioid antagonists and any others that might be found using the claimed method".

This rejection is traversed. Applicants respectfully submit that the phrases "opioid agonist" and "opioid antagonist" are phrases commonly used by those of skill in the art to refer to compounds which act to stimulate the opioid receptors of the brain (opioid agonists) and to block the opioid receptors (opioid antagonist) from stimulation. "Drugs that bind to physiological receptors and mimic the effects of the endogenous regulatory compounds are termed *agonists*. Other drugs bind to receptors and do not mimic, but interfere with, the binding of the endogenous agonist. Such compounds, which are themselves devoid of intrinsic regulatory activity, but which produce effects by inhibiting the action of an agonist (e.g., by competition for agonist binding sites), are termed *antagonists*." Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th Ed., McGraw-Hill Co., Inc. (1996) p. 30, attached herewith as Exhibit A.

Further, Applicants respectfully submit that the specification, as originally filed, provides supplemental support for the commonly used phrases "opioid agonist" and "opioid antagonist," and describes the functional relationship of these compounds. For example, with respect to the phrase "opioid agonist", paragraph [0002] of the specification recites:

> Opioids, also known as opioid agonists, are a group of drugs that exhibit opium or morphine-like properties. The opioids are employed primarily as moderate to strong analgesics, but have many other pharmacological effects as well, including drowsiness, respiratory depression, changes in mood and mental clouding without a resulting loss of consciousness. Opioids act as agonists, interacting with stereospecific and saturable binding sites in the brain and other tissues. Endogenous opioid-like peptides are present particularly in areas of the central nervous system that are presumed to be related to the perception of pain; to movement, mood and behavior, and to the regulation of neuroendocrinological functions. Opium contains more than twenty distinct alkaloids. Morphine, codeine and papaverine are included in this group.

Paragraph [0067] recites in part "[o]pioid agonists are thought to exert their agonist actions primarily at the mu receptor and to a lesser degree at the kappa receptor", and Applicants provide an exemplary list of opioid agonists at paragraph [0076]:

> Opioid analgesics which are useful in the present invention include all opioid agonists or mixed agonist-antagonists, partial agonists, including but not limited to alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum,

> pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, sufentanil, tilidine, tramadol, mixtures of any of the foregoing, salts of any of the foregoing, and the like.

With respect to the phrase "opioid antagonist", paragraph [0011] recites in part, "[p]harmacologically, opioid antagonists typically block or reverse all of the effect of opioid agonists. One use of opioid antagonists is as a once-a-day treatment of naltrexone to block euphoric effects that might be otherwise obtained upon administration of opioids to addicts." Applicants also provide an exemplary list of opioid antagonists at paragraph [0070], which recites that "cyclazocine and naltrexone, both of which have cyclopropylmethyl substitutions on the nitrogen" and "other opioid antagonists, including but not limited to naloxone, nalmephene, cyclazocine, and levallorphan can be utilized in accordance with the present invention."

Therefore, based on the general knowledge of one of ordinary skill in the art and the guidance (including definitions and numerous examples) provided in the specification, Applicants submit that the phrases "opioid agonist" and "opioid antagonist" are fully supported by the present specification. Accordingly, Applicants respectfully request that rejection under 35 U.S.C. § 112, first paragraph be removed.

B. Double Patenting Rejection

In the Office Action, the Examiner rejected claims 1, 3, 8-10, 12-27, 29-31 and 41-44 under 35 U.S.C. 101 as claiming the same invention as that of claims 1-11, 19-35 and 52-55 of U.S. Patent No. 6,375,957 to Kaiko et al. (hereinafter the '957 patent).

This rejection is respectfully traversed. Applicants submit that the presently amended claims recite:

> An oral dosage form, comprising an orally therapeutically effective amount of

> (A) **from about 2 mg to about 800 mg** of an opioid agonist,
>
> (B) acetaminophen, and
>
> (C) an opioid antagonist; the dosage form having a ratio of opioid antagonist to opioid agonist to acetaminophen that provides a combination product which is analgesically effective when the combination is administered orally, but which (i) is aversive in physically dependent human subjects when administered in the same amount **and** in a higher amount than said therapeutically effective amount; and (ii) maintains an analgesic effect but does not increase analgesic efficacy of the opioid agonist together with the acetaminophen relative to the same therapeutic amount of opioid analgesic together with the acetaminophen when administered to human patients without said opioid antagonist.

(Emphasis added).

Applicants point out that the present claims recite a dosage range comprising from about 2 mg to about 800 mg of an opioid agonist. In contrast, the claims of the '957 patent do not recite a dosage range for the opioid agonist. "A reliable test for double patenting under 35 U.S.C. 101 is whether a claim in the application could be literally infringed without literally infringing a corresponding claim in the patent." MPEP, 8th Ed. 4th Rev. § 804, citing *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970). Accordingly, Applicants submit that it is possible to literally infringe the claims of the '957 patent, without literally infringing the claims of the present application.

Applicants further note that the claims of the present application also recite that the ratio of the opioid agonist to opioid antagonist to acetaminophen is such that the dosage form will be aversive in physically dependent human subjects when administered in the same amount **and** in a higher amount than said therapeutically effective amount. In contrast, the claims of the '957 patent recite a ratio of the opioid agonist to opioid antagonist to acetaminophen such that the dosage form will be aversive in physically dependent human subjects when administered in the same amount **or** in a higher amount than said therapeutically effective amount.

As applied to the instant application, Applicants submit that, e.g., a dosage form having ratio of opioid agonist to opioid antagonist which is aversive in the same amount as the therapeutically effective amount, but not in a higher amount, would literally infringe the claims of the '957 patent, but would not infringe the present claims, as the present claims require that the amount be the same and higher than the therapeutically effective amount.

Accordingly, it is possible to literally infringe the corresponding claims in the patent without literally infringing the claims of the present application and Applicants respectfully request that the double patenting rejection be removed.

III. Conclusion

It is now believed that the above-referenced rejection has been obviated and it is respectfully requested that the rejection. It is believed that all claims are now in condition for allowance.

According to currently recommended Patent Office policy the Examiner is specifically authorized to contact the undersigned in the event that a telephonic interview will advance the prosecution of this application.

An early and favorable action is earnestly solicited.

Respectfully submitted,
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The PHARMACOLOGICAL BASIS OF THERAPEUTICS

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GOODMAN & GILMAN'S The PHARMACOLOGICAL BASIS OF THERAPEUTICS

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CHAPTER 2

PHARMACODYNAMICS

Mechanisms of Drug Action and the Relationship Between Drug Concentration and Effect

Elliott M. Ross

This chapter provides an introduction of the concept of receptors, the structural and functional families of receptors, and the interplay between the diverse signaling pathways activated by receptor occupancy. These introductory concepts are amplified in subsequent chapters detailing the structure and function of receptors for individual drug groups. The latter half of the chapter describes the historical development of receptor theory and presents means for quantifying receptor activation by agonists and blockade by antagonists. The functional relevance of partial agonists and inverse antagonists also is described as a prelude to the intentional development of mechanistically diverse drugs via classical or new combinatorial strategies.

Pharmacodynamics can be defined as the study of the biochemical and physiological effects of drugs and their mechanisms of action. The objectives of the analysis of drug action are to delineate the chemical or physical interactions between drug and target cell and to characterize the full sequence and scope of actions of each drug. Such a complete analysis provides the basis for both the rational therapeutic use of a drug and the design of new and superior therapeutic agents. Basic research in pharmacodynamics also provides fundamental insights into biochemical and physiological regulation.

MECHANISMS OF DRUG ACTION

The effects of most drugs result from their interaction with macromolecular components of the organism. These interactions alter the function of the pertinent component and thereby initiate the biochemical and physiological changes that are characteristic of the response to the drug. This concept—now obvious—had its origins in the experimental work of Ehrlich and Langley during the late nineteenth and early twentieth centuries. Ehrlich was struck by the high degree of chemical specificity for the antiparasitic and toxic effects of a variety of synthetic organic chemicals. Langley noted the ability of the South American arrow poison, curare, to inhibit the contraction of skeletal muscles caused by nicotine; however, the tissue remained responsive to direct electrical stimulation. The term *receptor* was coined to denote the component of the organism with which the chemical agent was presumed to interact.

The statement that the receptor for a drug can be any functional macromolecular component of the organism has several fundamental corollaries. One is that a drug potentially is capable of altering the rate at which any bodily function proceeds. Another is that drugs do not create effects, but instead modulate functions.

Drug Receptors

At least from a numerical standpoint, proteins form the most important class of drug receptors. Examples are the receptors for hormones, growth factors, and neurotransmitters, the enzymes of crucial metabolic or regulatory pathways (*e.g.*, dihydrofolate reductase, acetylcholinesterase), proteins involved in transport processes (*e.g.*, Na^+,K^+-ATPase), or proteins that serve structural roles (*e.g.*, tubulin). Specific binding properties of other cellular constituents also can be exploited. Thus, nucleic acids are important drug receptors, particularly for cancer chemotherapeutic agents.

A particularly important group of drug receptors are proteins that normally serve as receptors for endogenous regulatory ligands (*e.g.*, hormones, neurotransmitters). Many drugs act on such physiological receptors and are often particularly selective, because physiological receptors are specialized to recognize and respond to individual signal-

ing molecules with great selectivity. Drugs that bind to physiological receptors and mimic the effects of the endogenous regulatory compounds are termed *agonists.* Other drugs bind to receptors and do not mimic, but interfere with, the binding of the endogenous agonist. Such compounds, which are themselves devoid of intrinsic regulatory activity, but which produce effects by inhibiting the action of an agonist (*e.g.,* by competition for agonist binding sites), are termed *antagonists.* There are additional subtleties to drug classification. Thus, agents that are only partly as effective as agonists are termed *partial agonists,* and those that stabilize the receptor from undergoing productive agonist-independent conformational changes are termed *negative antagonists* or *inverse agonists.* (*See* below, "Quantitation of Drug–Receptor Interactions and Elicited Response.")

The binding of drugs to receptors can involve all known types of interactions—ionic, hydrogen bonding, hydrophobic, van der Waals, and covalent. In most interactions between drugs and receptors, it is likely that bonds of multiple types are important. If binding is covalent, the duration of drug action is frequently, but not necessarily, prolonged. Noncovalent interactions of high affinity also may appear to be essentially irreversible.

Structure–Activity Relationship and Drug Design. Both the affinity of a drug for its receptor and its intrinsic activity are determined by its chemical structure. This relationship is frequently quite stringent. Relatively minor modifications in the drug molecule may result in major changes in pharmacological properties.

Exploitation of structure–activity relationships has on many occasions led to the synthesis of valuable therapeutic agents. Because changes in molecular configuration need not alter all actions and effects of a drug equally, it is sometimes possible to develop a congener with a more favorable ratio of therapeutic to toxic effects, enhanced selectivity among different cells or tissues, or more acceptable secondary characteristics than those of the parent drug. Therapeutically useful antagonists of hormones or neurotransmitters have been developed by chemical modification of the structure of the physiological agonist. Minor modifications of structure also can have profound effects on the pharmacokinetic properties of drugs.

Given adequate information about both the molecular structures and the pharmacological activities of a relatively large group of congeners, it should be possible to identify those properties that are required for optimal action at the receptor—size, shape, the position and orientation of charged groups or hydrogen bond donors, and so on. Recent advances in computational chemistry, structural analysis of organic compounds, and the biochemical measurement of the primary actions of drugs at their receptors have enriched the quantit tion of structure–activity relationships and its use in drug desig (Kuntz, 1992; Schreiber, 1992). By accurately and quantitatively co relating the pharmacological activities of multiple drugs with the molecular structures—their overall shapes and the locations and or entations of chemically interactive groups on their surfaces—it possible to model accurately the structure of the binding site on t receptor. Such detailed models allow the informed design of in proved congeners or the *de novo* design of novel compounds that c bind to the receptor with improved selectivity, affinity, or regulato effect. Such considerations also allow computerized searching large chemical libraries for diverse compounds that, because of th overall three-dimensional structures, should act upon the receptor interest. Similar structure-based approaches also can be used to in prove pharmacokinetic properties of drugs (*see* Chapter 1).

Recent advances using the structures of receptors and of dru receptor complexes, determined at atomic resolution by X-ray cry tallography or nuclear magnetic resonance (NMR) spectroscopy, a even more helpful in the initial design of ligands. In cases where t structure of the entire receptor is unknown, it is often possible determine the conformation of the bound drug, thereby providing mirror image of the receptor's binding site. The ability to clone a express cDNAs that encode less abundant regulatory proteins and creasing success in the crystallization of membrane-bound prote offer great promise for drug design based on a detailed knowled of the drug binding site and the effect of drug binding on recep structure.

Ironically, advances in molecular biology that contribute structure-motivated drug design also have spawned powerful but tirely random searches for new drugs. In this approach, huge libra of randomly synthesized chemicals are generated either by synth chemistry or by genetically engineered microbes. A library the screened for pharmacologically active agents using mammalian c or microorganisms that have been engineered to express the rec tor of therapeutic interest and the associated biochemical machin necessary for detection of the receptor's response. Active compou initially discovered by such random screens then can be modified improved using knowledge of their structure–function relationsh

Cellular Sites of Drug Action. The sites at which a drug acts the extent of its action are determined by the localization and fu tional capacity of the specific receptors with which the drug in acts and the concentration of drug to which the receptor is expo Selective localization of drug action within the organism is th fore not necessarily dependent upon selective distribution of the d

If a drug acts on a receptor that serves functions commo most cells, its effects will be widespread. If the function is a one, the drug will be particularly difficult or dangerous to use. H ertheless, such a drug may be clinically important. Digitalis gl sides, important in the treatment of heart failure, are potent inhib of an ion transport process that is vital to most cells. As such, can cause widespread toxicity, and their margin of safety is dan ously low. Other examples could be cited, particularly in the are cancer chemotherapy.

If a drug interacts with receptors that are unique to only a types of differentiated cells, its effects are more specific. Hypo ically, the ideal drug would cause its therapeutic effect by suc action. Side effects would be minimized, but toxicity might no If the differentiated function were a vital one, this type of drug could be very dangerous. Some of the most lethal chemical ag known (*e.g.,* botulinus toxin) show such specificity and toxicity.